THE CONTRACEPTIVE PROGESTAGENS

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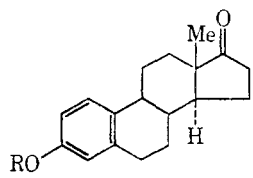
I. Introduction

The discovery of orally active steroidal progestagens by the pharmaceutical houses of Europe and the United States made possible the development of "the pill," which was first approved by the Food and Drug Administration in 1960. The time is ripe to review the chemistry of this group of hormonal steroids before they are displaced from their present key role in the control of human fertility by newer products invoking different contraceptive mechanisms. With some exceptions,[1] which are included for the sake of completeness, the review is concerned with progestagens that have been studied clinically as antifertility agents, with special emphasis laid upon those products that are presently employed in oral contraceptive (o.c.) preparations.

Pharmaceutical houses normally patent their discoveries prior to publication, which can often be delayed by months and even years. For this reason, the scientific literature cannot be used to establish priority of discovery. This has been done throughout the review on the basis of the application dates of the corresponding product patents. As the patent laws of America differ in some respects from those elsewhere, such application dates do not necessarily confer legal priority of discovery in the United States.

The story goes back to 1929 when Doisy, Veler, and Thayer[2] in the United States, and Butenandt[3] in Germany, independently discovered estrone (**1**, R = H) in pregnancy urine. Almost simultaneously, Marrian[4] isolated estriol (**2**) from the same source. A year earlier, Marrian[5] had obtained the biologically inactive pregnanediol (**3**) from pregnancy urine and, in working on the chemistry of the last two compounds



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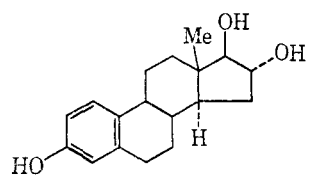

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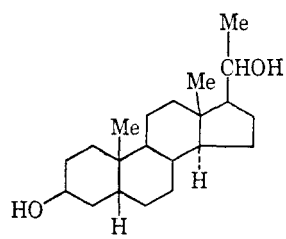

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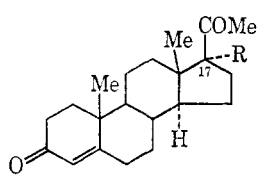
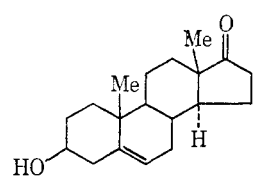
(**2** and **3**), had assumed a structural relationship between them.

In 1934, progesterone (**4**) was isolated from corpus luteum tissue by four independent groups of workers.[6] The hormone proved to be polymorphic (128 and 121°) and this fact added to the confusion of discovery. One other steroid, androstenolone, subsequently termed dehydroepiandrosterone (**5**) or



4, R = H
4a, R = OH
b, R = OAc
c, R = $OOCC_5H_{11}$



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DHA, needs to be mentioned. This weakly androgenic steroid was isolated from urine by Butenandt and Dannenbaum[7] in 1934, which was indeed a vintage year for discovery. DHA assumed immediate importance because of a suspected relationship to cholesterol, the estrogens, and the androgens. The relationship to cholesterol was brilliantly vindicated the

(1) Cyproterone acetate (**115**).

(2) (a) E. A. Doisy, C. D. Veler, and S. A. Thayer, *Amer. Phys.*, **90**, 329 (1929); (b) C. D. Veler, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **87**, 357 (1930).

(3) (a) A. Butenandt, *Naturwissenschaften*, **17**, 879 (1929); (b) A. Butenandt and E. von Ziegner, *Z. Physiol. Chem.*, **188**, 1 (1930).

(4) G. F. Marrian, *Biochem. J.*, **24**, 435, 1221 (1930).

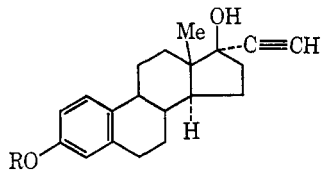
(5) G. F. Marrian, *ibid.*, **23**, 1090 (1929).

(6) (a) A. Butenandt, U. Westphal, and W. Hohlweg, *Z. Physiol. Chem.*, **227**, 84 (1934) (April); (b) K. H. Slotta, H. Ruschig, and E. Fels, *Ber.*, **67**, 1270 (1934) (July); (c) W. M. Allen and O. Wintersteiner, *Science*, **80**, 190 (1934) (August); O. Wintersteiner and W. M. Allen, *J. Biol. Chem.*, **107**, 321 (1934); (d) M. Hartmann and A. Wettstein, *Helv. Chim. Acta*, **17**, 1365 (1934) (October).

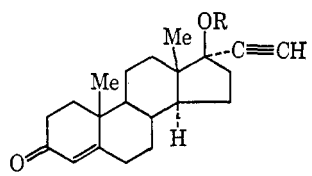
(7) (a) A. Butenandt and H. Dannenbaum, *Z. Physiol. Chem.*, **229**, 192 (1934); (b) A. Butenandt and K. Tscherning, *ibid.*, **229**, 167 (1934).

following year by its preparation by four groups[8] from cholesterol by oxidative degradation of the dibromide and by Oppenauer[8e] who prepared it from the plant sterol sitosterol.

The stage was set for the discovery of ethynylestradiol (**6**) and of ethisterone (**7**).

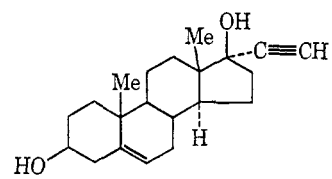


6, R = H
6a, R = Me



7, R = H
7a, R = Ac

Progesterone (**4**), unlike the estrogens, is only slightly active by mouth. In 1935, it was costly to produce; also the clinical dose was substantially greater than for the estrogens. There was consequently a need for a more active, and preferably orally active, product. DHA seemed to be an obvious starting point for research as it could be obtained with relative ease from cholesterol. As it was a C_{19} keto alcohol and progesterone was a C_{21} diketone, two independent groups[9a,b] conceived the idea of adding a 2-carbon moiety onto the carbonyl group of DHA with potassium acetylide to give the ethynyldiol (**8**). The following year, Inhoffen, Logemann, Hohlweg, and Serini,[10a] working in the laboratories of Schering A.-G., in Germany, converted the new diol (**8**) into the 3-oxo-Δ^4 de-



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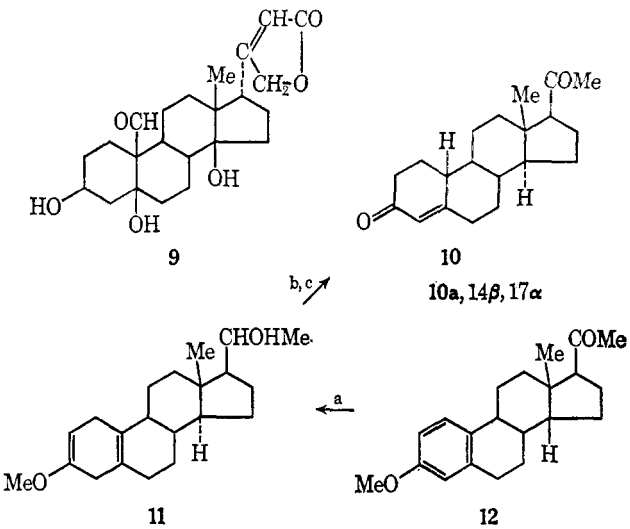
rivative (**7**) to which the name ethisterone was given. The product achieved immediate success as an orally active progestagen in spite of its significant androgenicity. The Schering group[10b] additionally condensed acetylene with estrone to obtain ethynylestradiol (**6**) which proved to be an immensely potent orally active estrogen which still remains unchallenged after 30 years of clinical use.

II. THE 19-NORPROGESTAGENS

There was now to be a break in discovery while nations engaged in World War II. In 1944, while the carnage was at its height, the late Maximilian Ehrenstein[11] reported the conversion of the heart glycoside strophanthidin (**9**) into the 19-norprogesterone (**10a**) in an overall yield of 0.7%. This product was the first example of the very important 19-norsteroid group (*vide infra*). It was not pure, yet even so its biological study revealed the surprising fact that it was as active and possibly more active than the parent progesterone (**4**) as a progestagen.

19-Norprogesterone
(Ehrenstein; Djerassi, Rosenkranz, and Miramontes)



9 10 10a, 14β, 17α 11 12

Reagents: a, modified Nelson–Wilds redn; b, HCl–MeOH; c, CrO_3–HAc

The discovery of **6**, **7**, and **10a** was a major breakthrough in hormone research, although its significance was not apparent at the time. The phrase "population explosion" had not yet been coined, nor was the world ready for the revolutionary concept of "the pill." When the smoke of the battle cleared, the center of research was no longer in the United States and in the research laboratories of a defeated Germany, but had shifted to the unruffled calm of Oxford where Birch was working on the reduction of phenolic ethers to their dihydro derivatives with sodium–ethanol in liquid ammonia. This reaction had first been described by Wooster[12] in the United States, but it was Birch and his school who had forged it into a powerful preparative tool for the organic chemist.

In 1949, Birch and Mukherji[13a] described the reduction of estrone glyceryl ether (**1**, R = $CH_2CHOHCH_2OH$) to a dihydro derivative (**13**) (R = $CH_2CHOHCH_2OH$) from which the 5(10)-en-3-one (**14**) was obtained. The following year Birch[13b] completed the sequence by converting **14** into 19-nortestosterone (**15**) using sodium ethoxide. In this publication, he expressed his intention of making steroid hormone analogs based upon the 19-nor skeletal structure. He had planned to make 19-norethisterone[14] (*vide infra*), but a concatenation of circumstances had led to a move to Australia with consequent delay in starting the project. This delay proved fatal to his plans and the initiative in exploiting the new reductive sequence was to pass to the United States where it had originally been discovered.

(8) (a) W. Schoeller, A. Serini, and M. Gehrke, *Naturwissenschaften*, **23**, 337 (1935), Schering A.-G., Berlin, W. Germany; (b) A. Butenandt, H. Dannenbaum, G. Hanische, and H. Kudszus, *Z. Physiol. Chem.*, **237**, 57 (1935); (c) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 986 (1935); (d) E. S. Wallis and E. Fernholz, *J. Amer. Chem. Soc.*, **57**, 1379 (1935); (e) R. V. Oppenauer, *Nature*, **135**, 1039 (1935).

(9) (a) J. Kathol, W. Logemann, and A. Serini, *Naturwissenschaften*, **25**, 682 (1937), Schering A.-G.; (b) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937).

(10) (a) H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Ber.*, **71**, 1029 (1938); (b) H. H. Inhoffen and W. Hohlweg, *Naturwissenschaften*, **26**, 96 (1938).

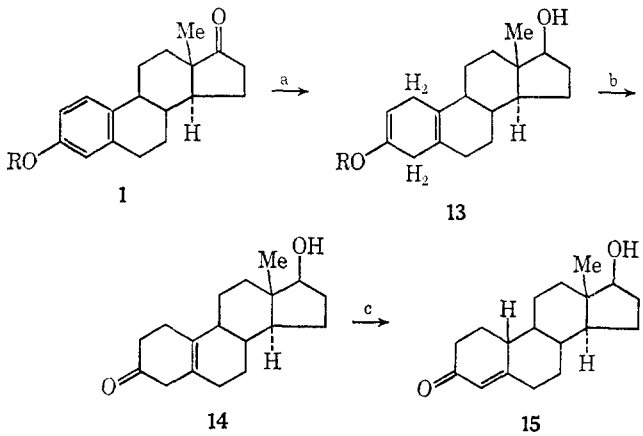
(11) (a) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944); (b) W. M. Allen and E. Ehrenstein, *Science*, **100**, 251 (1944); (c) G. W. Barber and M. Ehrenstein, *Justus Liebigs Ann. Chem.*, **603**, 89 (1957); (d) C. Djerassi and M. Ehrenstein, *ibid.*, **612**, 93 (1958).

(12) C. B. Wooster, U. S. Patent 2,182,242 (1939) to E. I. du Pont de Nemours & Co., Wilmington, Del., Application May 3, 1938; C. B. Wooster and K. L. Godfrey, *J. Amer. Chem. Soc.*, **59**, 596 (1937).

(13) (a) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1948), Dyson Perrins Laboratory, Oxford, U. K.; (b) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(14) Private communication from Professor A. J. Birch.

19-Nortestosterone
(Birch and Mukherji; Wilds and Nelson)



Reagents: a, Na(Li)–NH_3–EtOH; b, oxalic acid; c, NaOEt or HCl

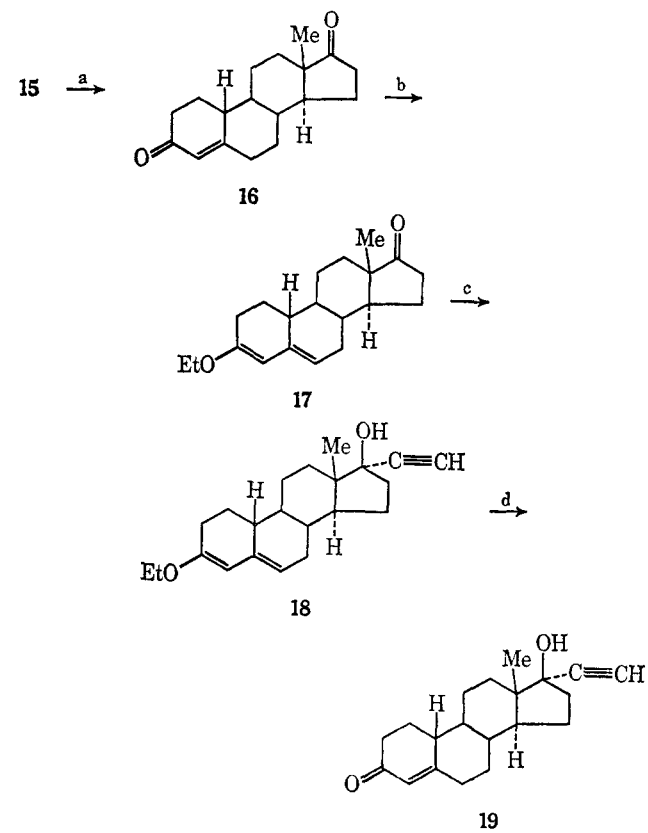
A major improvement in the Birch reduction was discovered by Wilds and Nelson[15] who replaced sodium by lithium and reversed the order of addition of the reagents. Their procedure consisted in adding lithium to the solution of the phenolic steroid in ether–liquid ammonia and then adding ethanol dropwise to the resulting dark blue solution. In this way, they converted the readily available estradiol methyl ether into 19-nortestosterone (**15**) in overall yields of 70–77% (based upon estrone).

Djerassi, Rosenkranz, and Miramontes,[16] working in the laboratories of Syntex S. A., in Mexico City, applied the Wilds and Nelson procedure in modified form to prepare 19-norprogesterone (**10**) from 17β-acetyl-3-methoxyestra-1,3,5(10)-triene (**12**). This compound, like the Ehrenstein isomer (**10a**), proved to be a more potent progestagen than the naturally occurring progesterone,[16,17a] and this result spurred them[17a] on to the preparation of norethindrone (19-norethisterone) (**19**). This was accomplished in November 1951. 19-Nortestosterone (**15**) was converted into the 3,17-dione **16** and thence *via* the 3-enol ether **17** into **19**. The process was later improved by Volkov and Rosenkranz[17b] who circumvented the need for the oxidation state (**15** → **16**) by protecting the 17-oxo group of estrone (**1**, R = H) as the 17-diethyl acetal prior to Birch reduction of the corresponding 3-methyl ether.

The following year, in 1952, Colton,[18a] working in the laboratories of G. D. Searle & Co. in Chicago, filed a patent claiming the key intermediate (**20**) for norethynodrel (**22**) which was itself described in 1953.[18b] These two 19-norsteroids (**22** and **19**) ushered in the oral contraceptive revolution that will always be linked with the names of Pincus and Rock.

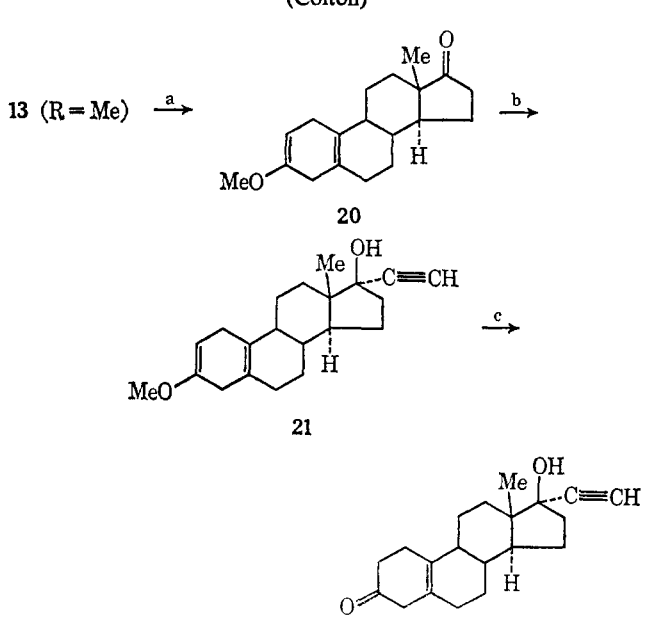
Other 19-norsteroidal progestagens followed this lead. In

Norethindrone
(Djerassi, Miramontes, and Rosenkranz)



Reagents: a, CrO_3; b, $CH(OEt)_3$–H^+; c, CH≡CK; d, H^+

Norethynodrel
(Colton)



Reagents: a, $Al(OPr^\beta)_3$–cyclohexanone; b, CH≡CK; c, HAc–MeOH

1954, Colton[19] prepared ethynodiol (17α-ethynylestr-4-ene-

(15) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360, 5366 (1953).

(16) C. Djerassi, G. Rosenkranz, and L. E. Miramontes, U. S. Patent 2,759,951 (1956) (claims priority June 4, 1951 (Mexico)), Application Oct 5, 1951.

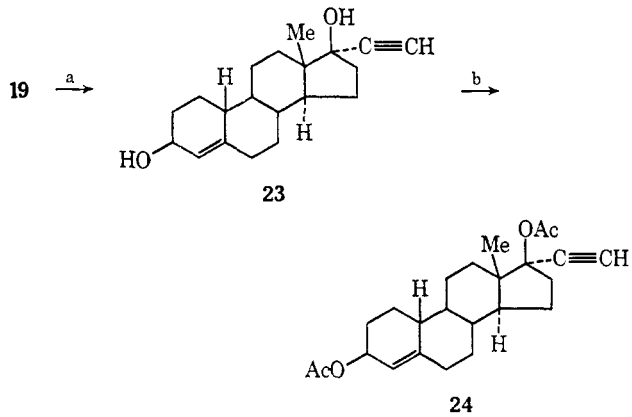
(17) (a) C. Djerassi, L. E. Miramontes, and G. Rosenkranz, U. S. Patent 2,744,122 (1956) (claims priority Nov 22, 1951 (Mexico)), Application Nov 12, 1952; (b) E. Volkov and G. Rosenkranz, U. S. Patent 2,940,990 (1960), Application May 22, 1956.

(18) (a) F. B. Colton, U. S. Patent 2,655,518 (1953), Application May 7, 1952; (b) U. S. Patent 2,691,028 (1954), Application May 25, 1953; U. S. Patent 2,725,389 (1955), Application Aug 31, 1953.

(19) F. B. Colton, British Patent 776,427 (1957), Application Oct 25, 1954; U. S. Patent 2,843,609 (1958) (claims priority Oct 11, 1955); *cf.* U. S. Patent 2,843,609 (1958), Application Oct 10, 1956; P. D. Klimestra and F. B. Colton, *Steroids*, **10**, 411 (1957).

3β,17β-diol) (**23**) by reduction of **19** with sodium borohydride

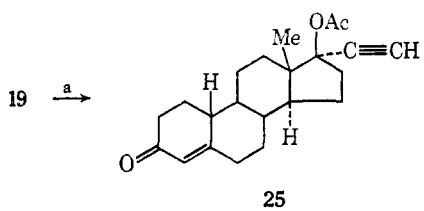
Ethynodiol diacetate
(Colton)



Reagents: a, $NaBH_4$; b, acetylation

in methanol. The product (**19**) was also prepared independently by Sondheimer and Klibansky[20] by an essentially similar route. Its diacetate (**24**) proved to be a valuable antifertility agent, but 11 years[21] was to elapse before it was to be introduced into the United States. Engelfried, Kaspar, Popper, and Schenck,[22] working in the laboratories of Schering A.-G.

Norethisterone acetate
(Engelfried, Kaspar, Popper, and Schenck)



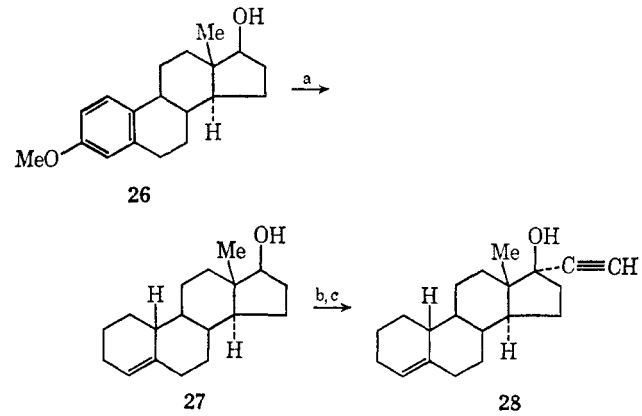
Reagent: a, Ac_2O–pTs

in Berlin, extended their earlier studies on the acetylation of ethisterone (*vide infra*) to 19-norethisterone (**19**) and obtained the 17-acetate (**25**). Szpilfogel[23a] of Organon in Holland had meanwhile discovered that reduction of estradiol 3-methyl ether (**26**) with lithium in ethylamine leads to the 3-deoxy 19-nor alcohol (**27**) from which the 3-deoxy analog (**28**) of norethindrone was prepared, and to which the name lynestrenol was given. Szpilfogel[23b] subsequently introduced an alternative route to **27** in which **15** was converted into the 3-ethylene thioketal and the last compound was reduced to the 3-deoxy alcohol (**27**) by sodium in liquid ammonia.

III. 17α-Acetoxyprogesterone

Parallel with these developments, a new chemistry of progesterone was being developed that was destined to yield progestagens as potent as any derived from 19-nortestosterone.

Lynestrenol
(Szpilfogel)



Reagents: a, Li–$EtNH_2$; b, CrO_3; c, CH≡CK

In 1941, Pfiffner and North,[24] working in the laboratories of Parke, Davis and Co., isolated 17α-hydroxyprogesterone (**4a**) from adrenal glands and reported that it was inactive in the Clauberg assay (for progestational activity) by the intramuscular route. Attempts to acetylate the 17α-hydroxy group in this compound were not successful. Some 10 years later, Turner,[25a] working at the Rice Institute in Texas, and Huang-Minlon, Wilson, Wendler, and Tishler,[26] of Merck and Co., Inc., independently showed that it was possible to acetylate such hindered C_{17}-hydroxyl groups under forcing conditions. Turner used 3β,17α-dihydroxy-5α-pregnan-20-one as his model compound, and the following year[25b] reported the extension of his method to 17α-hydroxyprogesterone to give the 17-acetate (**4b**). The Merck group employed 3α,17α,21-trihydroxypregnane-11,20-dione. Almost immediately afterwards, Oliveto, Gerold, and Hershberg[27] of the Schering Corp. (U.S.A.) and Moffett and Anderson[28] of The Upjohn Co. independently reported the preparation of 17α-acetoxyprogesterone (**4b**).

At about this time, the question of depot injections of hormones was becoming increasingly important, and such companies as Ciba, Organon, and Schering A.-G. were devoting resources to the study, *inter alia*, of testosterone and estradiol esters in order to find long-acting preparations. In 1954, Junkmann[29] of Schering A.-G. reported that ethisterone 17-acetate (**7a**), a progenitor of the Schering progestagen 19-norethisterone acetate (**25**) referred to above, was very soluble in organic solvents in contrast to its highly insoluble parent (**7**) but did not show much prolongation of progestational activity on injection. A similar situation existed with 17α-acetoxyprogesterone (**4b**). The corresponding caproate (**4c**), in contrast, proved to be suitable for use in a depot preparation. Surprisingly, the German company did not examine their 17α-hydroxyprogesterone esters for oral activity. It

(20) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

(21) Introduced into the United States for the cyclic control of ovulation in 1966.

(22) O. Engelfried, E. Kaspar, A. Popper, and M. Schenck, German Patent 1,017,166 (1957), Application June 16, 1956.

(23) (a) S. A. Szpilfogel, Dutch Patent 89,824 (1958), Application April 10, 1957 (Organon N. V., Oss, Netherlands); (b) S. A. Szpilfogel, German Patent 1,119,858 (1960), Application Jan 13, 1959; M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind. (London)*, 905 (1959).

(24) J. J. Pfiffner and H. B. North, *J. Biol. Chem.*, **139**, 855 (1941).

(25) (a) R. B. Turner, *J. Amer. Chem. Soc.*, **74**, 4220 (1952); (b) *ibid.*, **75**, 3489 (1953).

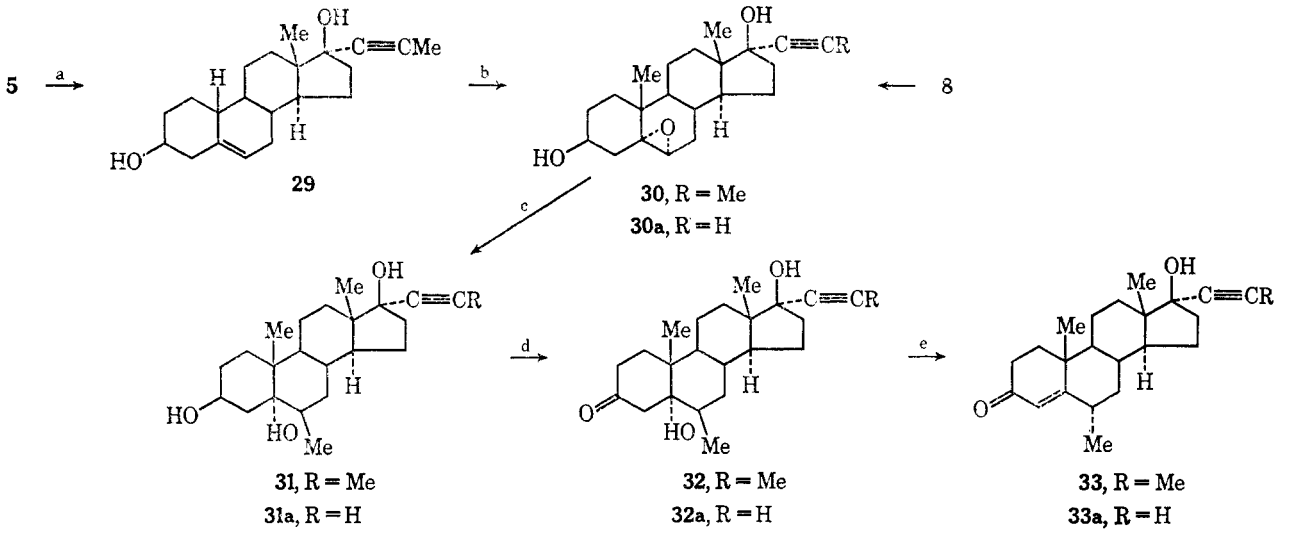
(26) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *ibid.*, **74**, 5394 (1952).

(27) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *Arch. Biochem. Biophys.*, **43**, 234 (1953) (Schering Corp., Bloomfield, N. J.).

(28) R. B. Moffett and H. V. Anderson, *J. Amer. Chem. Soc.*, **76**, 747 (1954).

(29) K. Junkmann, *Arch. Exp. Pathol. Pharmakol.*, **223**, 244 (1954); E. Kaspar, K. H. Pawlowski, K. Junkmann, and M. Schenck, U. S. Patent 2,753,360 (1956), Application Nov 30, 1954 (Schering A.-G., W. Germany).

Dimethisterone (33)
(Barton, Burn, Cooley, Ellis, Petrow, and Stuart-Webb)



Reagents: a, MeC≡CMgBr; b, $PhCO_3H$; c, MeMgBr; d, CrO_3; e, H^+

fell to the Upjohn group[30] to carry out this study and discover the oral progestational activity of 17α-acetoxyprogesterone (**4b**). This result was destined to play an important role in o.c. development.

IV. The 6-Methylated Progestagens

The stage was set for the next big advance—the discovery and exploitation of the 6-methylated derivatives of 17α-acetoxyprogesterone. The pharmaceutical houses of Europe and the United States struggled to dominate this field. The intensity of the struggle may be gauged by the fact that in the United States patent priorities were sometimes decided by margins of only 24 hr.

In 1954, Burstein, Dorfman, and Nadel[31] found that hydrocortisone was metabolically deactivated in both guinea pig and man by conversion into 6β-hydroxyhydrocortisone. At the time, the reviewer was working in the research laboratories of the former British Drug Houses Ltd.,[32] in London, U. K., which company made a range of steroid hormones including ethisterone (**7**). The last compound had begun to lose its luster in the light of the newer 19-norprogestagens. It was, therefore, not surprising that the reviewer was given the task of finding a more potent progestagen which additionally would not belong to the 19-nor series, as the company lacked the raw materials to manufacture this group of compounds. In furtherance of this assignment, he conceived the idea of preventing metabolic degradation of steroid hormones by methylation at C_6, hoping thereby to achieve an increase in potency. The first experiments were directed toward the preparation of 6-methylethisterone from 17α-ethynylandrost-5-ene-3β,17β-diol (**8**). This was converted into the 5α,6α-epoxide (**30a**) and thence into 6α-methylethisterone (**33a**).[33] Biological study of this compound (**33a**)[33a] revealed that it was some 6.5 times more potent than ethisterone in the (rabbit) Clauberg assay. Surprisingly, the 6β isomer was much less active.

Following this gratifying result, the U. K. group turned its attention to the systematic preparation of 6-methylated steroid hormones and to the ω alkylation of the ethynyl side chains of **7**, **19**, and **33a**. Dimethisterone (**33**) resulted from this program[33b] and proved to be some 12 times more active than its unmethylated parent (**7**) in the Clauberg assay. Dimethisterone formed the progestagenic component in the first sequential oral contraceptive to be issued in the United States.

The series of transformations, exemplified by **8** → **30** → **33**, was also developed independently by other groups[34] at about the same time, and became a standard method for converting steroidal 3β-hydroxy-5-ene intermediates into the corresponding 6α-methyl-4-en-3-ones.

As diosgenin (**43**) was their major raw material for steroid hormone manufacture, the U. K. group in 1956 began the systematic study of methods for the production of 6-methyldiosgenin (**43a**). They planned, *inter alia*, to convert it into the versatile intermediate **49** and thence into such products as 17α-acetoxy-6α-methylprogesterone (**38**). Unbeknown to them, six other research groups had simultaneously conceived the idea of making the last compound and were working vigorously toward its fulfillment. Insofar as the United States is concerned, patent priority for the discovery of this im-

(30) The Upjohn Co., British Patent 848,881 (1960), Application Dec 27, 1955; M. E. Davis and G. L. Wied, *J. Clin. Endocrinol. Metab.*, **17**, 1237 (1957).

(31) S. Burstein, R. I. Dorfman, and E. M. Nadel, *Fed. Proc.*, **13**, 188 (1954); *Arch. Biochem. Biophys.*, **53**, 307 (1954).

(32) The British Drug Houses Ltd., later The BDH Group Ltd., had origins going back to 1714. It was taken over by, and absorbed into, The Glaxo Group Ltd., in 1968.

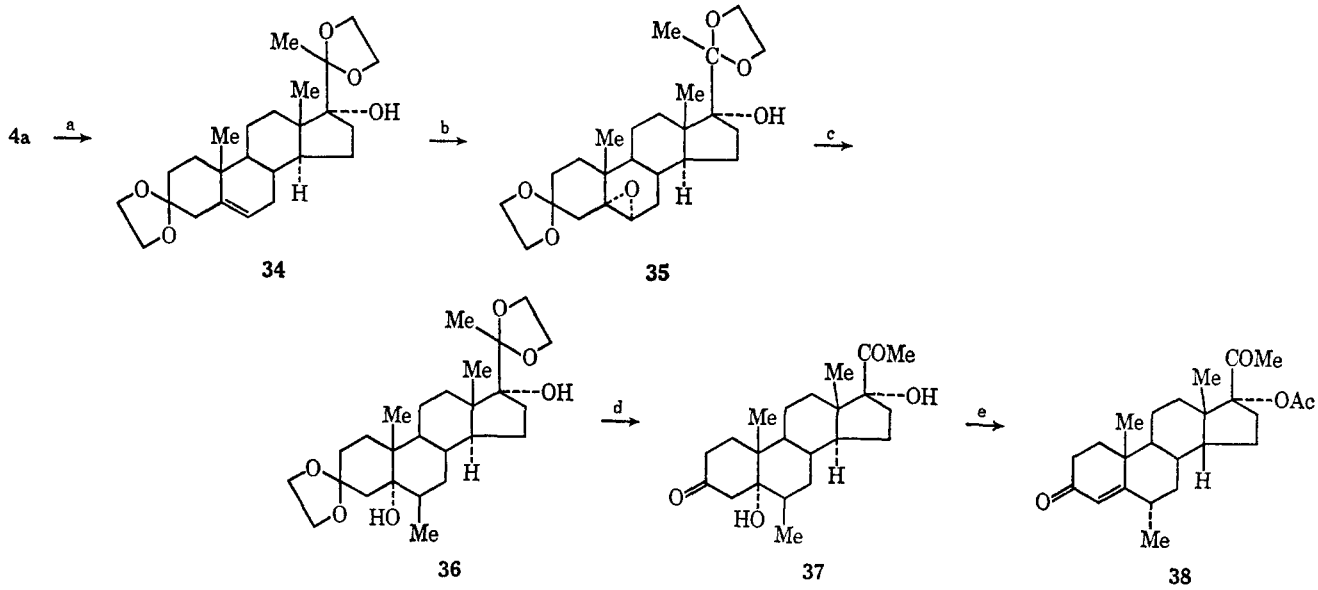
(33) W. J. Adams, V. Petrow, B. Ellis, and I. A. Stuart-Webb, British Patents 801,201, 801,202 (1958), Application June 2, 1955; W. J. Adams, B. Ellis, V. Petrow, and I. A. Stuart-Webb, British Patent 802,003 (1958), Application June 5, 1955; British Patent 802,004 (1958), Application June 20, 1955; British Patent 802,005 (1958), Application June 22, 1955. This and subsequent British Patents by the U. K. group were assigned to The British Drug Houses, Ltd., London.

(33a) A. David, F. Hartley, D. R. Millson, and V. Petrow, *J. Pharm. Pharmacol.*, **9**, 929 (1957).

(33b) S. P. Barton, D. Burn, G. Cooley, B. Ellis, V. Petrow, and I. A. Stuart-Webb, British Patent 841,887 (1960), Application Jan 25, 1957; B. Ellis, V. Petrow, M. Stansfield, and I. A. Stuart-Webb, British Patent 842,678 (1960), Application May 21, 1957; see also ref 33 and 33a.

(34) See ref 37, 39, and 75.

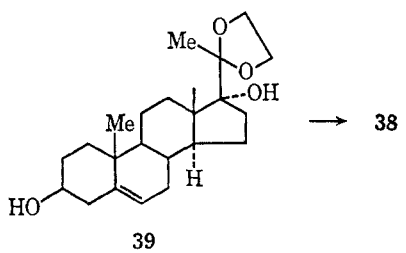
Medroxyprogesterone acetate
(Spero: Babcock, Gutsell, Herr, Hogg, Stucki, Barnes, and Dulin)



Reagents: a, $(CH_2OH)_2$–pTs; b, $MeCO_3H$; c, MeMgBr; d, H_2SO_4; e, HCl–$CHCl_3$, Ac_2O–HAc–pTs

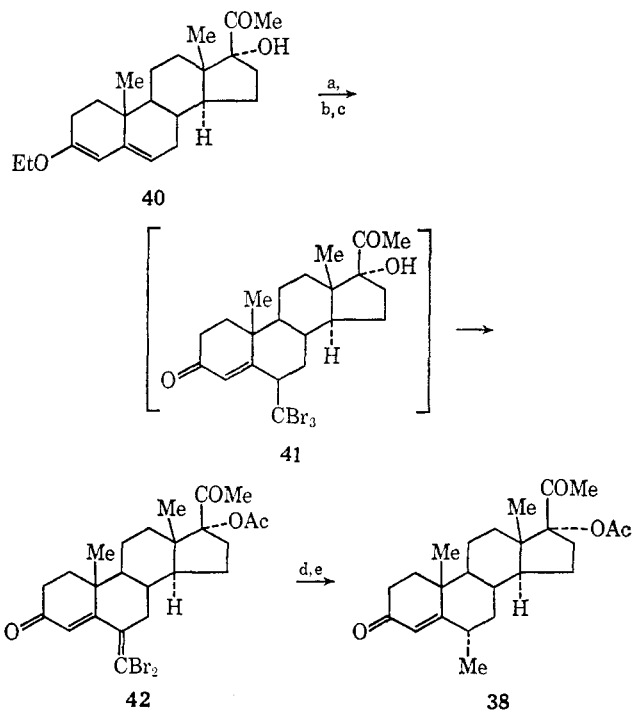
portant product rests with Spero,[35] of the Upjohn group, who prepared it by the so-called "ketal route" in which an appropriate 3-oxo-4-ene (**4a**) is converted into the corresponding 3-ethylenedioxy-5-ene (**34**), and thence *via* the 5α,6α-epoxide (**35**) into the 5α-hydroxy-6β-methyl derivative (**36**). Subsequent reactions (**37** → **38**) follow the pattern previously established for dimethisterone. Essentially the same route was independently developed by the Syntex group[36] and by the Farmitalia group[37] who additionally used the 3β-hydroxy-Δ⁵ intermediate (**39**) as starting material, employing transformations exemplified by **29** → **33**.

Medroxyprogesterone acetate
(Camerino, Modelli, Patelli, Sala, and Baldratti;
Ringold, Ruelas, Batres, and Djerassi)



At about the same time, Godtfredsen and Liisberg[38] discovered an entirely new approach to 6α-methylated steroid ketones. Yields were variable, but in the reviewer's laboratory the process proved to be exceptionally useful for the preparation of medroxyprogesterone acetate (**38**). The Danish workers found that the 3-enol ether (**40**) of 17α-hydroxyprogesterone reacted with carbon tetrabromide in dioxane–pyridine solution at room temperature to give an intermediate (probably **41**) which passed smoothly into the dibromomethylene derivative (**42**) on heating in pyridine solution. Reduction of the last compound, followed by epimerization of admixed 6β-methyl isomer with acid, gave **38** in high overall yield. It is perhaps relevant at this point to refer to the work of Rug-

Medroxyprogesterone acetate
(Godtfredsen and Liisberg)



Reagents: a, CBr_4–pyridine–dioxane; b, boil filtrate from a; c, HAc–Ac_2O–pTs; d, Pd–$SrCO_3$–H_2; e, H^+

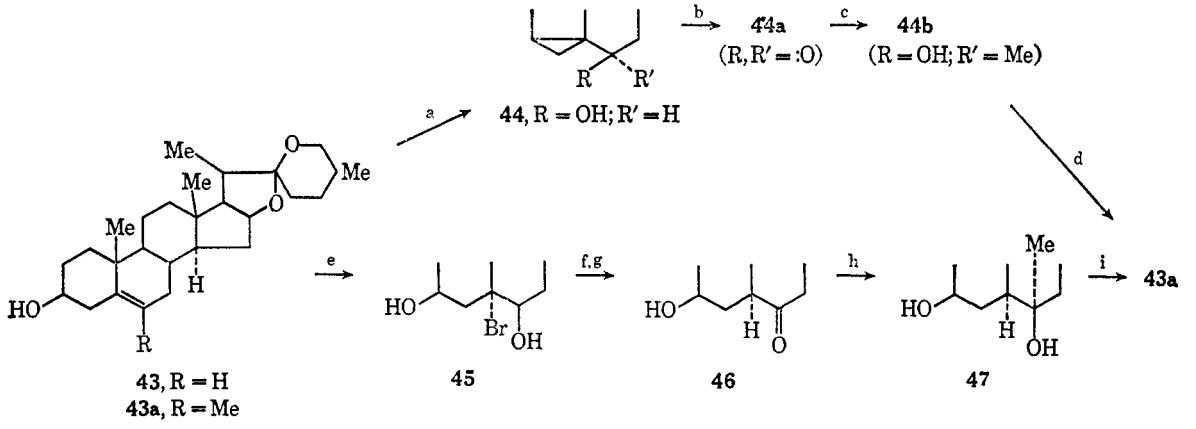
(35) G. B. Spero, U. S. Patent 3,377,364 (1968), Application Nov 23, 1956 and Sept 23, 1957; see also J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Amer. Chem. Soc.*, **80**, 2904 (1958).

(36) Derwent 5379; French Patent 1,295,307, Application Sept 8, 1956.

(37) B. Camerino, R. Modelli, B. Patelli, G. Sala, and G. Baldratti, U. S. Patent 3,061,616 (1962) (claims priority April 24, 1958 (G. B.)), Farmaceutici Italia, Milan, Italy; see also H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 3712 (1959).

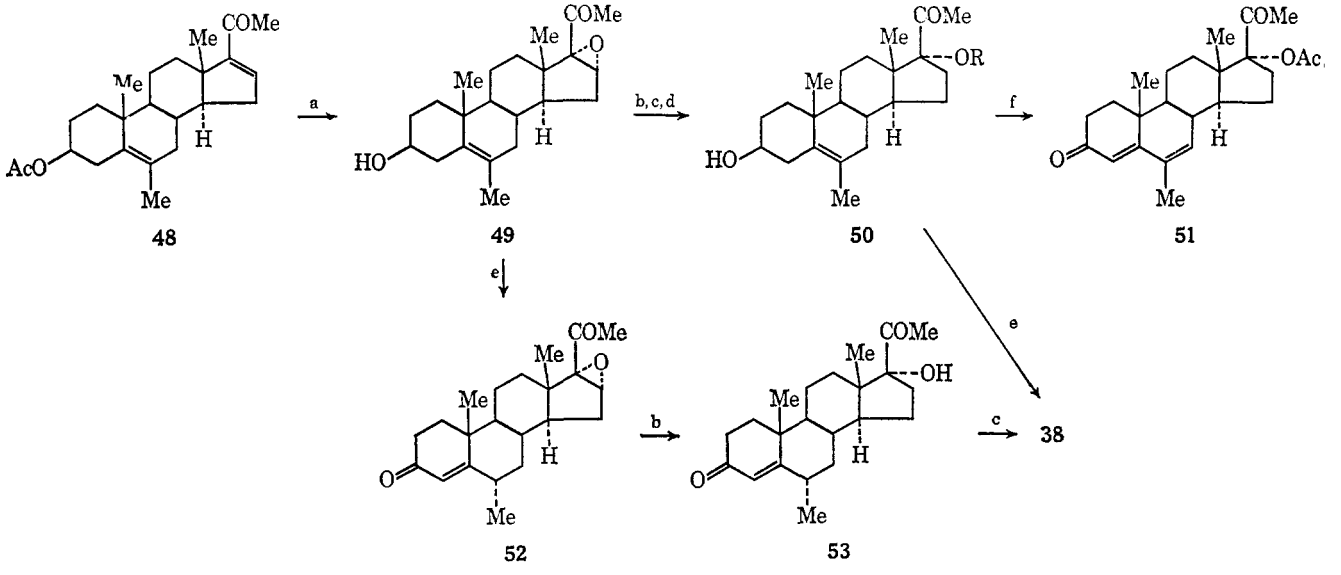
(38) W. O. Godtfredsen and S. Liisberg, U. S. Patent 3,047,566 (1962) (claims priority June 13, 1958 (G. B.)); U. S. Patent 2,996,523 (1961) (claims priority Aug 8, 1958 (G. B.)), Løvens Kemiske Fabrik, Ballerup, Denmark.

6-Methyldiosgenin
(Petrow, Stuart-Webb, and Williamson)



Reagents: a, KAc–Me Et ketone upon the 3-tosylate; b, CrO_3–pyridine; c, MeMgI; d, H_2SO_4–HAc; e, NBA–$HClO_4$–dioxane; f, CrO_3–pyridine; g, Zn dust–HAc; h, MeMgI; i, $SOCl_2$–pyridine

Medroxyprogesterone acetate and megestrol acetate
(Petrow, Stuart-Webb, and Williamson; Miramontes, Romero, and Fritsche; Loken and Flores; and Kirk, Petrow, and Williamson)



Reagents: a, H_2O_2–NaOH–MeOH; b, HI and Raney Ni; c, Ac_2O–pTs; d, HCl–MeOH; e, $Al(OPr^{\beta})_3$–cyclohexanone; f, $Al(OBu^{t})_3$–*p*benzoquinone

gieri and Ferrari[39] who employed the 17-cyanohydrin of dehydroepiandrosterone as starting material for medroxyprogesterone acetate. The 17α-tetrahydropyranyl ether of its 5α,6α-epoxide was treated with methylmagnesium bromide to give 6β-methyl-3β,5α,17α-trihydroxypregnan-20-one, readily converted into **38**.

As mentioned above, the U. K. group began work in 1956 on the production of 6-methyldiosgenin (**43a**) as a potential raw material for **38** and in 1957 developed the first practical route[40] to this valuable intermediate. Diosgenin (**43**) was submitted to the "3,5-cyclorearrangement" to give **44**, which was oxidized to the 3,5-cyclo-6-one (**44a**), from which **43a** was obtained by a Grignard reaction followed by dehydration. An improved process[41] was subsequently developed in which **43** was converted into the 6-one (**45**), from which 6-methyldiosgenin was obtained by a Grignard reaction followed by a Darzens dehydration. The preparation of **43a** from the 5α,6α-epoxide of **43** *via* a 5α-hydroxy-6β-methyl intermediate, *cf.* **29** → **31**,[42] proved to be inferior to the foregoing methods owing to troublesome formation of the Δ^4 isomer.[43]

With 6-methyldiosgenin (**43a**) available in quantity, the U. K. group turned to its exploitation as a raw material for 6-methylated steroid hormone production. Its degradation to 3β-acetoxy-6-methylpregnane-5,6-dien-20-one (**48**)[44] offered no difficulty, and using this versatile intermediate, Stuart-Webb readily converted it by the anticipated route (**48** → **49** → **50** → **38**) into medroxyprogesterone acetate

(39) P. de Ruggieri and C. Ferrari, British Patent 866,656 (1961), Application Sept 29, 1958; British Patent 863,522 (1961), Application Sept 29, 1958, Ormonoterapie Richter S.p.A., Milan, Italy.

(40) V. Petrow and I. A. Stuart-Webb, British Patent 841,870 (1960), Application May 3, 1957.

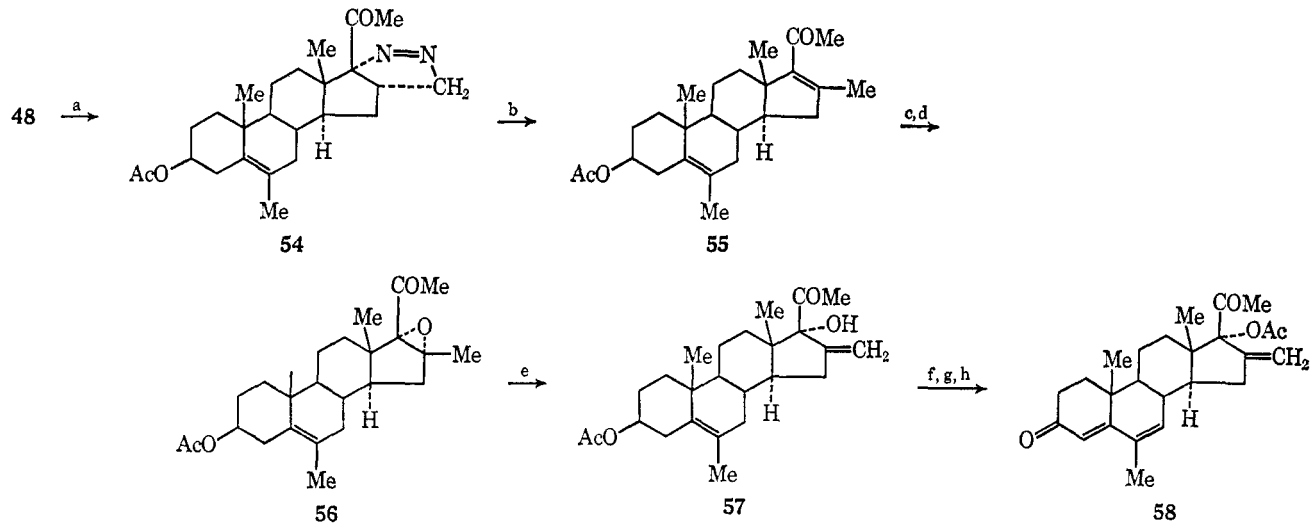
(41) V. Petrow and D. M. Williamson, British Patent 851,741 (1960), Application Aug 28, 1957.

(42) D. N. Kirk and V. Petrow, British Patent 843,664 (1960), Application Oct 9, 1957; D. N. Kirk, V. Petrow, and M. H. Thomson, British Patent 861,007 (1960), Application Jan 16, 1958; *cf.* ref 46.

(43) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(44) V. Petrow and D. M. Williamson, British Patent 851,742 (1960), Application Aug 28, 1957; see also L. E. Miramontes, M. A. Romero, and F. A. Farjat, U. S. Patent 3,000,914 (1961), Application May 28, 1958, G. D. Searle & Co.

Melengestrol acetate
(Petrow and Williamson; Kirk, Petrow, and Williamson; Babcock and Campbell)



Reagents: a, CH_2N_2; b, Bu_2O, reflux, c, H_2O_2–NaOH–MeOH; d, Ac_2O–py; e, HBr–HAc; f, Ac_2O–pTs; g, MeOH–HCl; h, $Al(OBu^t)_3$–*p*-benzoquinone

(**38**).[45] Simultaneously, the Searle group[46] prepared **38** by the alternative route **49** → **52** → **53** → **38**.

The preparation of megestrol acetate (**51**) by the U. K. group[47] came about by chance. The preparation of **38** from **50** had been accomplished, and the group was rather at a loss on what to do next. As **50** (R = Ac) was available in relative quantity, the reviewer suggested that it be oxidized with aluminum *t*-butoxide–*p*-benzoquinone to the 4,6-dien-3-one and added the rider that the product (**51**) was unlikely to be of much value as 6-dehydroprogesterone was a weaker progestagen than progesterone.[48] It was a surprise to the group when **51** was found[49] to be the most active antiovulatory compound (in the rabbit) available at the time. As may be expected, **51** was prepared almost simultaneously by other groups.[50] Megestrol acetate formed the progestagenic component in the first British oral contraceptive.

Following success with the 6-methylated progestagens **33**, **38**, and **51**, the reviewer turned to the partial synthesis of 6,16-dimethylated types. In retrospect, the decision to make these compounds was not entirely rational as 16α-methylprogesterone, previously made by Marker and Crooks,[51] had been found[52] to be less potent than its parent. Yet the impetus stemming from success brooked no argument or delay. 6α-Methylpregnadienolone acetate (**48**) was submitted to the Azarello reaction[53] to yield **54** and thence **55**, which passed smoothly into the 16α,17α-epoxide. The last compound was acetylated (to give **56**) and the acetate treated with HBr. In accordance with normal practice, the total product so obtained was treated without purification with Raney nickel to give crystalline material believed to be a 17α-hydroxy-16ξ-methylpregnane. As described elsewhere,[54] it was ultimately identified as the 17α-hydroxy-16-methylene derivative (**57**) and converted by oxidation into melengestrol acetate (**58**).[55] Almost simultaneously, Babcock and Campbell filed a patent claiming the preparation of **58** by an almost identical route.[56] The interests of the two groups parted at this point. The U. K. workers, in conjunction with Liggins,[57] of Auckland, New Zealand, examined the use of melengestrol acetate as an oral contraceptive and menostat.[58] The U. S. group,[59] in contrast, developed its veterinary applications.

In 1960, Kirk, working in the reviewer's laboratory, discovered the application of the Vilsmeier reaction to steroidal enol ethers (**59**), thereby making available for the first time a new series of extremely versatile steroidal intermediates. These were immediately exploited by the U. K. group who were able to develop, *inter alia*, a new and highly attractive route[60] to megestrol acetate (**51**).

(45) V. Petrow, British Patents 852,683, 852,684 (1960), Application Oct 2, 1957.

(46) B. Löken and H. Flores, U. S. Patent 2,875,198 (1959), Application May 27, 1958; L. E. Miramontes, M. A. Romero, and O. Fritsche, U. S. Patent 2,878,247 (1958), Application Sept 27, 1957, G. D. Searle & Co., Mexico City, Mexico, assignee.

(47) D. N. Kirk, V. Petrow, and D. M. Williamson, British Patent 870,286 (1961), Application Nov 4, 1958.

(48) C. Meystre, E. Tschopp, and A. Wettstein, *Helv. Chim. Acta*, **31**, 1463 (1948); A. Wettstein, *ibid.*, **23**, 388 (1940), Ciba, Basel, Switzerland.

(49) A. David, K. Edwards, K. P. Fellowes, and J. M. Plummer, *J. Reprod. Fert.*, **5**, 331 (1963).

(50) R. M. Dodson and P. B. Sollman, U. S. Patent 2,891,079 (1959), Application Jan 23, 1959, G. D. Searle & Co.; B. Camerino and B. Patelli, British Patent 896,980 (1962), Application Nov 20, 1959, Farmaceutici Italia, Milan, Italy; P. de Ruggieri, C. Ferrari, and C. Gandolfi, Belgian Patent 579,052, Application May 27, 1959, Ormonaterapie Richter; J. A. Campbell and J. C. Babcock, U. S. Patent 3,143,556 (1964), Application Oct 5, 1960, The Upjohn Co.

(51) R. E. Marker and H. M. Crooks, Jr., *J. Amer. Chem. Soc.*, **64**, 1280 (1942).

(52) Unpublished data reported by Dr. A. David when at The British Drug Houses Ltd.

(53) See A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(54) D. N. Kirk, V. Petrow, M. Stansfield, and D. M. Williamson, *J. Chem. Soc.*, 2385 (1960); D. N. Kirk, V. Petrow, M. Stansfield, and D. M. Williamson, British Patent 857,114 (1960), Application Aug 11, 1958.

(55) V. Petrow and D. M. Williamson, British Patent 850,423 (1960), Application July 9, 1958; D. N. Kirk, V. Petrow, and D. M. Williamson, British Patent 886,619 (1960), Application Aug 28, 1959.

(56) J. C. Babcock and J. A. Campbell, U. S. Patent 3,359,287 (1967), Application Nov 16, 1959.

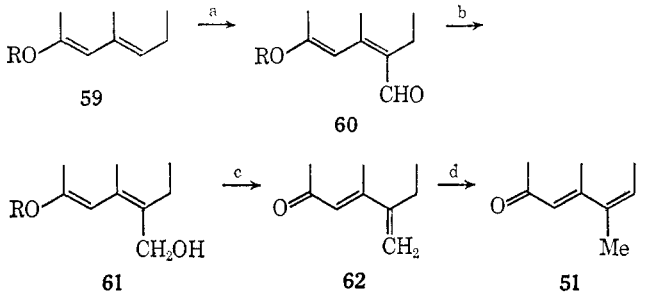
(57) G. C. Liggins, lecture at Hanmer Springs, N. Z., 1964 (unpublished).

(58) V. Petrow, *Advan. Sci.*, **2**, 22 (1965); *Essays Biochem.*, **2**, 117 (1966).

(59) J. C. Babcock and J. A. Campbell, U. S. Patent 3,417,182 (1968), Application June 17, 1964.

(60) D. N. Kirk and V. Petrow, British Patents 929,983; 929,984, 929,985 (1963), Application Nov 7, 1960; V. Petrow, British Patent 957,222 (1964), Application Sept 27, 1961; D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, **20**, 597 (1964); D. Burn, D. N. Kirk, and V. Petrow, *ibid.*, **21**, 1619 (1965).

6-Methylation
(Kirk and Petrow)



Reagents: a, $COCl_2$–DMF; b, $NaBH_4$; c, H^+; d, PdC–cyclohexene

V. Chlormadinone Acetate

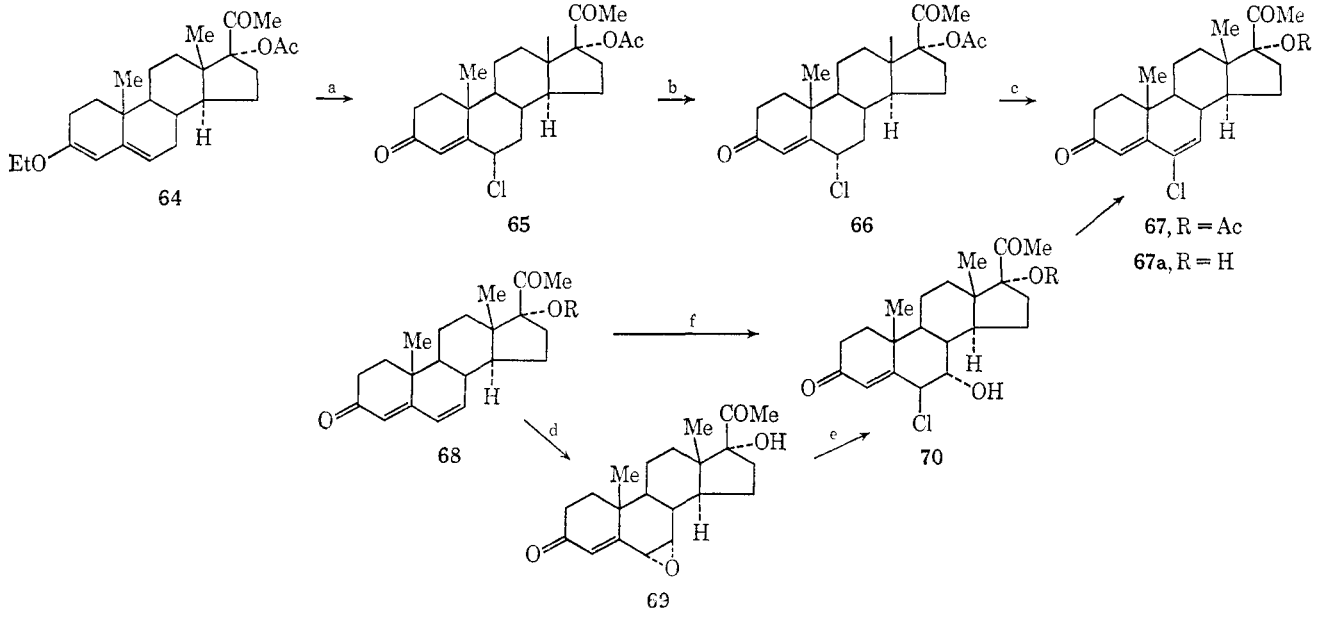
Parallel with these developments in the 6-methyl series, the Syntex group in Mexico and E. Merck A.-G. in Germany were developing the chemistry of the 6-halogenated steroid hormones. In 1958, both groups achieved the preparation of chlormadinone acetate (**67**). The Syntex group prepared this important progestagen from the 3-ethyl enol ether (**64**) of 17α-acetoxyprogesterone by reaction with N-chlorosuccinimide to give the 6β-halo derivative (**65**), followed by epimerization at C_6[61] and Δ^6 dehydrogenation.[62] Brückner,[63] in contrast, started with 6-dehydro-17α-hydroxyprogesterone (**68**, R = H) which was converted into the 6α,7α-epoxide (**69**). yielded **67**. The intermediate chlorohydrin (**70**, R = Ac) was subsequently prepared by Ringold, Alvarez, and Orr[64] from **68** (R = Ac) by direct treatment with chromyl chloride and converted into **67** by HCl–chloroform.

VI. Algestone Acetophenide, Quingestanol Acetate, and Norgestrel

In addition to megestrol and chlormadinone acetates, an entirely new type of progestagen was prepared in 1958 by Fried, of the Olin Mathieson Chemical Corp. The U. K. group had earlier studied routes to 16-hydroxylated steroidal hormones and had made[65] the significant observation that controlled oxidation of 16-dehydroprogesterone (**71**) with potassium permanganate in aqueous acetone–acetic acid gives the 16α,17α-glycol (**72**) in excellent yield, and had characterized this product as the acetonide (**73**). Fried recognized the potential significance of **73** as an antifertility agent and ultimately prepared[66] and developed the corresponding acetophenide (**74**) as the progestagenic component in a parenteral contraceptive preparation.

Ercoli and Ruggieri had discovered a few years previously a novel ether exchange process.[67] The following year Ercoli[68] had applied this reaction to the preparation of the 3-cyclopentyl enol ether of 19-norethisterone acetate. The product, quingestanol acetate (**76**), proved to be an extremely effective

Chlormadinone acetate
(Ringold and Bowers; Brückner)



Reagents: a, N-chlorosuccinimide; b, HCl–HAc; c, chloranil; d, peracetic acid; e, HCl–HAc; f, CrO_2Cl_2–$HClO_3$

The last compound was treated with HCl–HAc, when it passed smoothly into **67a**, presumably *via* the chlorohydrin (**70**, R = H). Enforced acetylation with Ac_2O–HAc–pTs progestagen–contraceptive agent, particularly when administered orally in oil.

(61) H. J. Ringold, E. Batres, G. Rosenkranz, O. Mancera, and A. Bowers, U. S. Patent 3,322,796 (1967) (claims priority Nov 4, 1957).

(62) H. J. Ringold and A. Bowers, U. S. Patent 3,485,852 (1969), Application C.I.P. Ser. No. 826,119, July 10, 1959; Ser. No. 25,238, April 28, 1960; and Ser. No. 104,001, April 19, 1961. This Application, Dec 13, 1963, Ser. No. 330,234, claims priority to Mexico, July 10, 1959 and Nov 13, 1958, Syntex Corp.; H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, **81**, 3485 (1959).

(63) K. Brückner, German Patent 1,075,114 (1960), Application April 29, 1958, E. Merck Akt., Darmstadt, Germany.

(64) H. J. Ringold, F. Alvarez, and J. C. Orr, U. S. Patent 3,076,823 (1963), Application July 3, 1961.

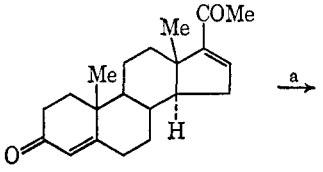
(65) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4373 (1955).

(66) J. Fried, U. S. Patent 2,941,997 (1960), Application Nov 18, 1958, Olin Mathieson Chemical Corp., New York, N. Y.; see also J. Fried and P. Diassi, U. S. Patent 3,008,958 (1961), Application Jan 27, 1961.

(67) A. Ercoli and P. de Ruggieri, U. S. Patent 2,835,667 (1958), Application June 20, 1955, Francisco Vismara S.p.A., Milan, Italy, now an International Division of Warner-Lambert, Morris Plains, N. J.

(68) A. Ercoli, British Patent 911,428 (1962), Application May 4, 1959.

16α,17α-Dihydroxyprogesterone acetonide
(Cooley, Ellis, Hartley, and Petrow)



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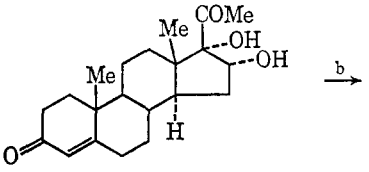

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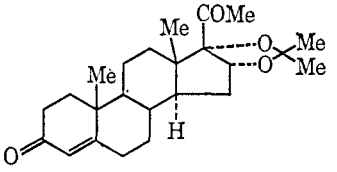
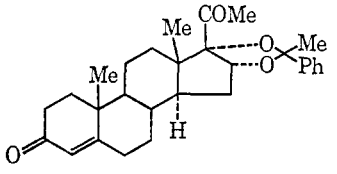


73

Reagents: a, $KMnO_4$–aq acetone; b, Me_2CO–HCl

Algestone acetophenide (Fried)

72 →

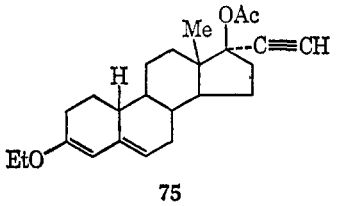


74

Reagent: MeCOPh–$HClO_4$

Quingestanol acetate
(Ercoli and Ruggieri)

25 →



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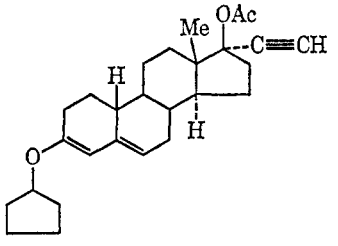


76

Reagents: a, $CH(OEt)_3$–pTs; b, ether exchange

It was now the turn of the synthetical chemist to make his unique contribution to the oral contraceptive field. The early pioneers of total synthesis, such as Johnson, Nazarow, and Robinson, had paved the way to this development, but the "population explosion" was still some years away. It fell to Herschel Smith, a pupil of Birch, who in his turn had been a pupil of Robinson, to take up the legacy of the past and with its help discover the first of the totally synthetical progestagens. The product, norgestrel (**86**), was prepared by Hughes and Smith[69] as indicated in the scheme **77** → **86**. It represents the last member of the "first generation contraceptive progestagens."

VII. Other Progestagens Examined as Contraceptive Agents

The present review would be incomplete without a reference to some of the other progestagens prepared in the late 50's–early 60's which were studied as antifertility agents and which form part of the background knowledge from which the second generation products are presently being evolved.

The Dutch firm of Philips-Dufar had long specialized in the manufacture of vitamin D_3 by irradiation of ergosterol. Small wonder then that their research division had turned to their own specialized irradiation products as raw materials for the partial synthesis of steroid hormones. By degrading lumisterol (**87**) as indicated in the scheme **87** → **91**, Reerink, Westerhof, and Schöler[70] obtained 6-dehydro-9β-10α-progesterone (6-dehydroretroprogesterone, dydrogesterone) (**91**) which was found to be an excellent progestational agent. Surprisingly, the compound has little value as an ovulation inhibitor, and its predominant action at presently used dose levels seems to be upon the uterine endometrium.

Chlorethynyl progestagens such as **94** (R = Cl) resulted from work by three groups. The Eli Lilly Co. group[71] examined the halogenation of norethynodrel (**22** or **93**, R = H) with pyridine bromide–hydrobromide in pyridine solution and obtained 17α-ethynyl-17β-hydroxyestra-4,9-dien-3-one (**94**, R = H) which proved to be more effective than 19-norethisterone in reducing the fecundity of rats. At the same time, the group at Merck, Sharp and Dohme[72] in the U. S. A. and the U. K. group[73] were studying substituted 17α-ethynyl steroids. Both groups treated **92** with lithium chloracetylide to obtain **93** (R = Cl) which the American group then converted into **94** (R = Cl).[72] The last compound was studied by them in detail but did not achieve clinical acceptability.

A somewhat different type of progestagen was developed by Deghenghi, of Ayerst Research Laboratories in Canada. Plattner, Heusser, and Herzig[74] had previously converted pregnenolone into 17α-methylprogesterone by a multistep process involving the Favorskii rearrangement of the 17α-bromo 20-ketone. Using this structure as a starting point, Deghenghi grafted onto it the 6-methyl-Δ^6 moiety to give the highly potent progestagen medrogestone (**100**). Its preparation

(69) H. Smith, British Patent 1,051,836 (1966), Application April 20, 1965; G. A. Hughes and H. Smith, British Patent 975,593 (1960), Application Feb 19, 1960; British Patent 991,592 (1965), Application Feb 19, 1960; British Patent 991,594 (1965), Application Feb 19, 1960; British Patent 1,010,052 (1965), Application Sept 22, 1960; British Patent 1,010,053 (1965), Application Sept 22, 1960; British Patent 1,041,278 (1966), Application Oct 19, 1961; British Patent 1,041,280 (1966), Application Oct 19, 1961.

(70) E. H. Reerink, P. Westerhof, and H. L. Schöler, U. S. Patent 3,198,792 (1965), Application June 12, 1962.

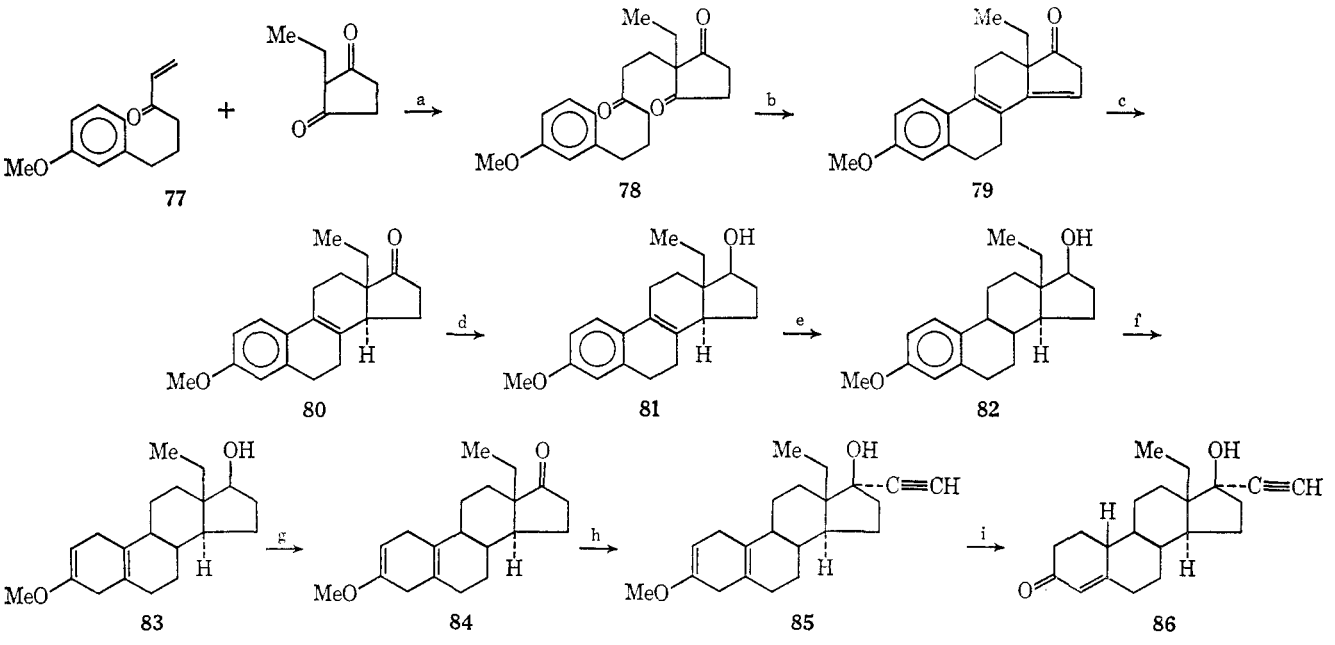
(71) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kray, and R. T. Rapala, *J. Amer. Chem. Soc.*, 82, 2402 (1960).

(72) J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarrett, and S. L. Steelman, *ibid.*, 83, 4663 (1961); J. H. Fried and T. S. Bry, U. S. Patent 3,072,646 (1963), Application March 2, 1961; U. S. Patent 3,096,353 (1963), Application Aug 3, 1961; L. H. Sarrett, T. S. Bry, J. Fried, A. E. Oberster, and R. E. Beyler, U. S. Patent 3,389,153 (1968), Application Aug 13, 1965.

(73) V. Petrow, C. M. Burgess, and P. Feather, British Patent 919,565 (1963), Application Aug 4, 1960.

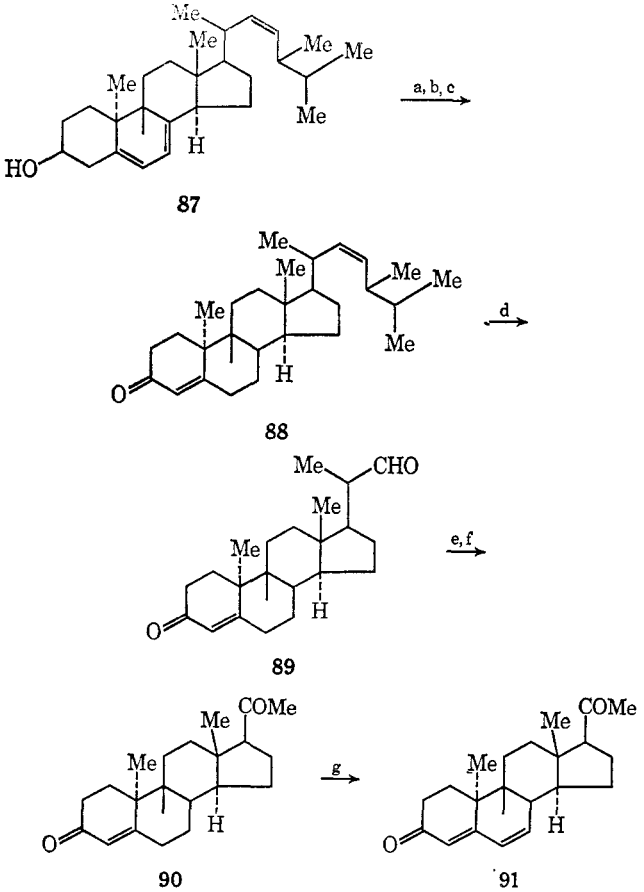
(74) Pl. A. Plattner, H. Heusser, and P. Th. Herzig, *Helv. Chim. Acta* 32, 272 (1948); H. Heusser, Ch. R. Engel, P. Th. Herzig, and Pl. A. Plattner, *Helv. Chim. Acta*, 33, 2229 (1950).

Norgestrel
(Hughes and Smith)



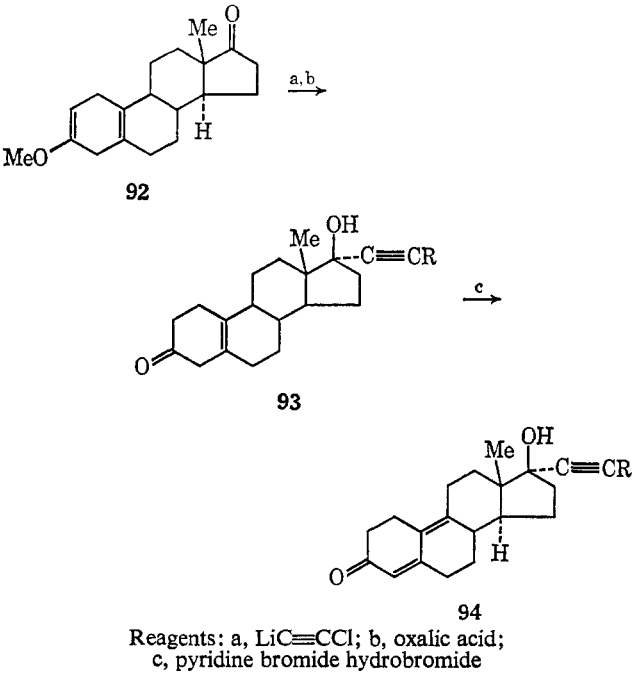
Reagents: a, KOH–MeOH; b, pTs; c, Pd–$CaCO_3$–H_2; d, $NaBH_4$–MeOH; e, K–NH_3–THF; f, Li–EtOH–NH_3; g, $Al(OPr^{\beta})_3$; h, $LiC{\equiv}CH$–$(CH_2NH_2)_2$; i, HCl–MeOH

Dydrogesterone
(Reerink, Westerhof, and Schöler)



Reagents: a, Oppenauer; b, HCl–PrOH; c, Li–NH_3; d, O_3–pyridine–CH_2Cl_2; e, piperidine–pTs; f, Na_2CrO_4–HAc; g, chloranil–Bu^tOH

17α-Chloroethynyl-17β-hydroxyestra-4,9-dien-3-one
(Fried and Bry; Petrow, Burgess, and Feather)



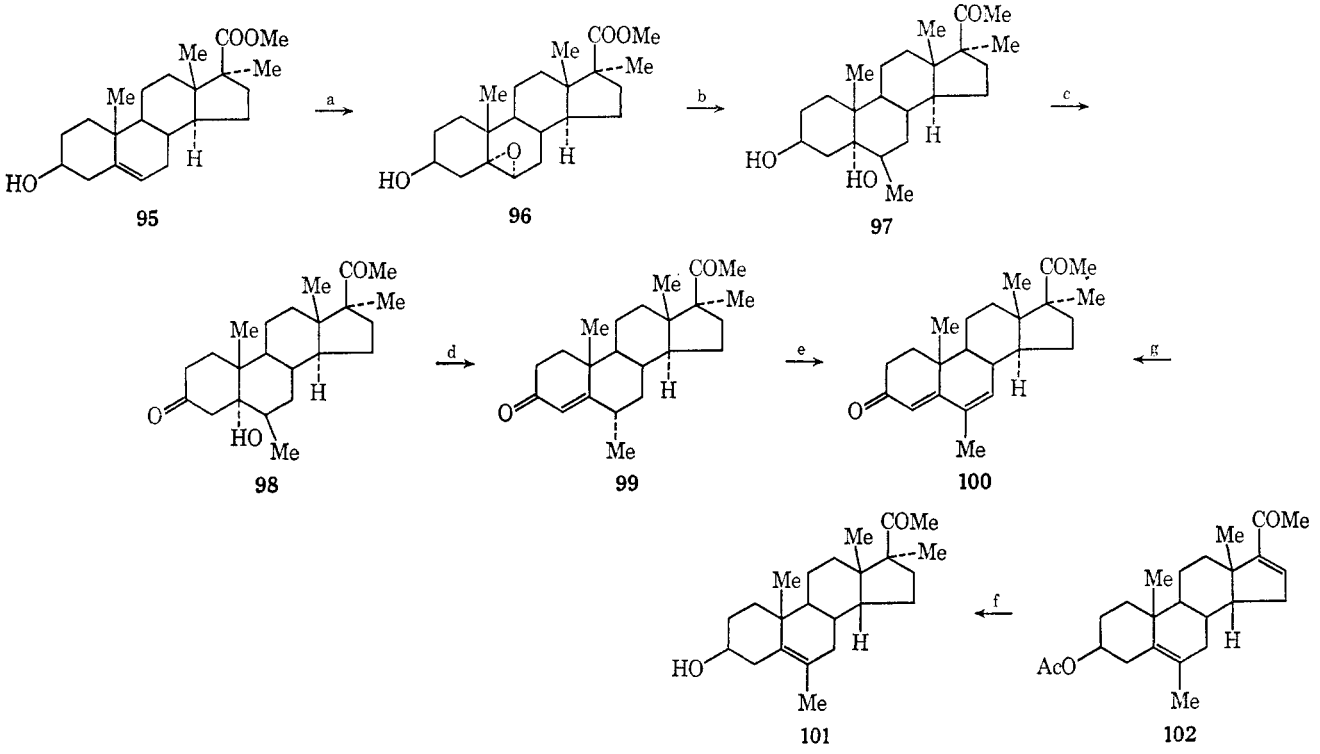
Reagents: a, $LiC{\equiv}CCl$; b, oxalic acid; c, pyridine bromide hydrobromide

provided certain novel features. In his first process, Deghenghi treated the 5α-6α-epoxide (**96**) of 17α-methyl cholenic acid methyl ester with excess methylmagnesium iodide to obtain the key intermediate (**97**) in one operation, which was then converted into medrogestone (**100**) by conventional procedures.[75] Subsequently, Deghenghi[76] achieved the direct C_{17}

(75) R. Deghenghi, U. S. Patent 3,133,916 (1964) (claims priority June 2, 1960 (Switzerland)), American Home Products Corp., New York, N. Y.

(76) R. Deghenghi, U. S. Patent 3,219,672 (1965) (claims priority March 23, 1962 (Canada)).

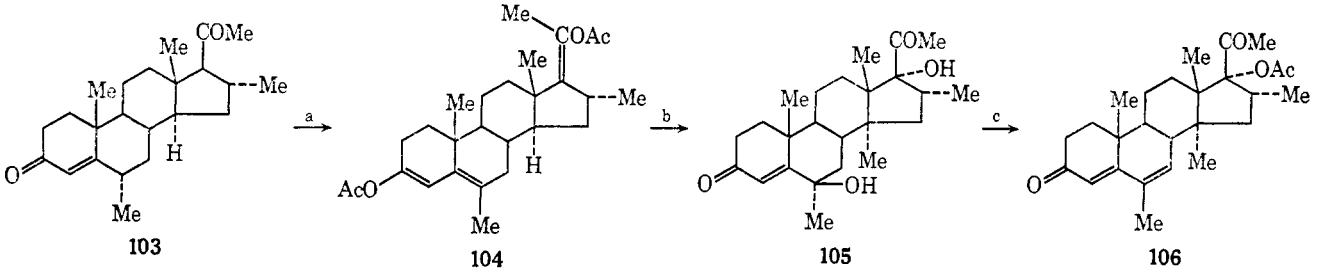
Medrogestone
(Deghenghi)



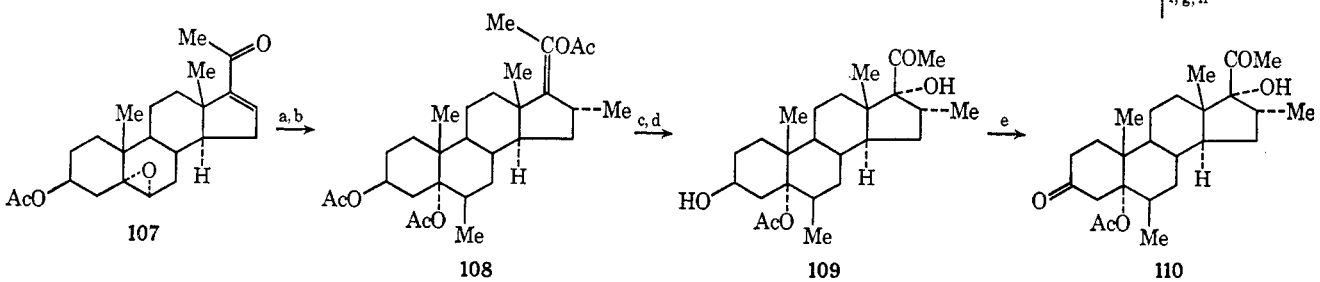
Reagents: a, peracetic acid; b, MeMgI; c, CrO_3; d, $SOCl_2$–pyridine; e, chloranil; f, Li–NH_3 and then MeI; g, $Al(OPr^{\beta})_3$–chloranil–cyclohexanone

17α-Acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione

(Barton, Ellis, and Petrow)



(Graber, Meyers, Hickman, Borochoff, and Odell)



Reagents (Barton, *et al.*): a, Ac_2O–pTs; b, monoperphthalic acid; c, Ac_2O–$HClO_4$—(Graber, *et al.*): a, MeMgBr–Cu_2Cl_2; b, Ac_2O; c, $PhCO_3H$; d, K_2CO_3–MeOH; e, CrO_3–aq H_2SO_4; f, HCl–EtOH; g, HAc–Ac_2O–pTs; h, chloranil

methylation of pregn-16-en-17-ones (**102** → **101**) (see also ref 77) and, using this reaction, developed an alternative and more attractive route to this progestagen (**100**).

One other dimethylprogesterone derivative achieved clinical status as an antifertility agent during the period under review. The compound 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione (**106**) was prepared by the U. K. group and by Graber and Myers of General Mills in the U. S. Its patent status in the U. S. has still to be established.

(77) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (*London*), 118 (1963), American Cyanamid Co., Pearl River, N. Y.

Kirk, Petrow, and Williamson[78a] had previously prepared 6α,16α-dimethylprogesterone (**103**) for clinical study in premenstrual tension. Barton, Ellis, and Petrow[78b] converted the last compound (**103**) into the dienol diacetate (**104**), which on treatment with peracid gave **105**. Enforced acetylation of the last compound gave 17α-acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione (**106**), which was found[78b] to be approximately equipotent with **51** in the (rabbit) Clauberg assay. Surprisingly, the corresponding 16β-methyl isomer was virtually devoid of biological activity. Petrow and Williamson[79] subsequently developed an improved route to **106**.

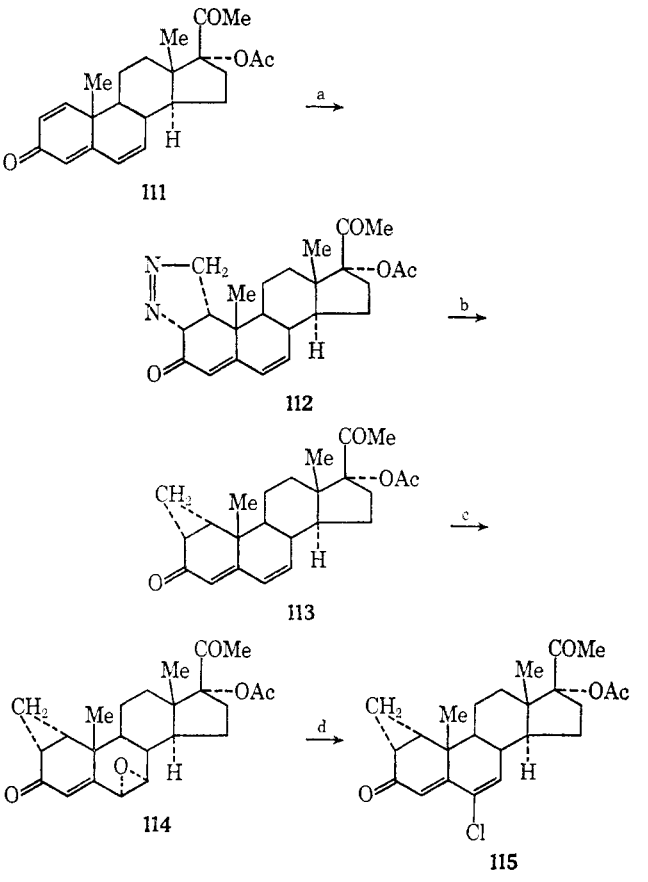
In Mexico, Djerassi and Ringold[80] claimed the preparation of 17α-hydroxy-6,16α-dimethylpregnenolone from the epoxide **56** by treatment with hydrobromic acid to give the "pure bromohydrin" followed by its reduction with Raney nickel. In the reviewer's laboratory this reaction has invariably yielded the 16-methylene derivative (**57**). Direct comparison of the two sets of data is not possible as melting points and analyses are not quoted in the Mexican work.

Graber and Meyers[81a] have a series of pending patent applications dealing with the partial synthesis of **106**, so that it is impossible at this time to give a balanced review of their contribution. The group has reported[81b] a process based upon the 5α,6α-epoxide (**107**) of pregnadienolone acetate which involves an ingenious route to the 21-enol acetate and thence as indicated in the diagram to **106**.

One further compound needs mention in order to complete the review of first generation progestagens and their congeners. Wiechert, Kaspar, and Schenck[82] extended the chlormadinone acetate series[70] to its 1α,2α-methylene derivative (**115**) to which the name cyproterone acetate was given. This potent progestagen is of particular interest as an antiandrogen.

Second generation progestagens are now being evolved or are under clinical study as antifertility agents in their own right. *Inter alia*, these include Ciba 31,458Ba (**116**)[83] which is the 19-nor analog of **45**, anagestone acetate (**117**),[84] which is the 3-deoxy analog of **38**, and clomegestone acetate (**118**),[85] which stems from **67** and **106**. Xinogestone[86] (**119**) is the 19-nor analog of a metabolite of progesterone, which has additionally been esterified in order to convert it into a form suitable for use in a depot preparation.

Cyproterone acetate
(Weichert, Kaspar, and Schenck)



Reagents: a, CH_2N_2; b, $HClO_4$; c, $PhCO_3H$; d, HCl–HAc

VIII. Biological Activity

The possibility of inducing temporary sterility in the female by ovarian extracts was predicted by Haberland[87] some 13 years before the isolation of progesterone. In 1937, Makepeace, Weinstein, and Friedman[88] proved the validity of this concept by showing that progesterone would inhibit ovulation after mating in the estrogen primed rabbit. Inhibition of ovulation in women by estrogen was developed by Kurzrok[89] and the "sequential method" of fertility control was enunciated by Fuller Albright[90] in 1945. There the matter rested. Cheap, orally active progestagens were not available at the time, nor was there interest in fertility control by hormonal products.

It is ironical that the development of oral contraception had *de facto* origins in the work of Rock, Garcia, and Pincus[91] on unexplained infertility in women, which they treated with daily oral progesterone (300 mg) administered from the 5th day of menstruation to the 25th day inclusive. Ovulation was generally inhibited, but there was a considerable incidence of breakthrough bleeding (BTB) which it was hoped to control with added estrogen. With the concurrent development of

(78) (a) D. N. Kirk, V. Petrow, and D. M. Williamson, British Patent 841,003 (1960), Application March 7, 1958; (b) S. P. Barton, B. Ellis, and V. Petrow, British Patent 884,544 (1961), Application Oct 12, 1959; B. Ellis, S. P. Hall, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 22 (1962).

(79) V. Petrow and D. M. Williamson, British Patent 920,521 (1963), Application Aug 25, 1960.

(80) C. Djerassi and H. J. Ringold, U. S. Patent 3,158,629 (1964) (claims priority June 27, 1958 (Mexico)).

(81) (a) R. P. Graber, M. B. Meyers, L. G. Hickman, E. H. Borochoff, and A. D. Odell, *J. Med. Chem.*, 7, 540 (1964), General Mills, Minneapolis, Minn.; (b) Belgian Patent 613,688 (1962), Application Feb 9, 1961.

(82) R. Wiechert, E. Kaspar, and M. Schenck, German Patent 1,072,991 (1960), Application Oct 25, 1958; R. Wiechert, German Patent 1,158,966 (1963), Application April 29, 1961, Schering A.-G.

(83) P. A. Desaulles and C. Krähenbühl, *Acta Endocrinol. (Copenhagen), Suppl.*, **119**, 143 (1967); A. Wettstein, G. Anner, K. Hensler, J. Kalvoda, and P. Wieland, U. S. Patent 3,250,792 (1966) (claims priority July 14, 1961 (Switzerland)), Ciba Corp., New York, N. Y.

(84) I. Scheer, U. S. Patent 3,162,629 (1964), Application June 6, 1962; G. Karmas and I. Scheer, U. S. Patent 3,192,202 (1965), Application March 12, 1964; I. Scheer, U. S. Patent 3,390,157 (1968), Application July 24, 1961; U. S. Patent 3,390,157 (1968), Application June 25, 1968, Ortho Research Foundation, Raritan, N. J.

(85) R. Wiechert, Belgian Patent 621,981 (1963), Application Sept 1, 1961, Schering A.-G.

(86) Organon; *cf.* S. G. Heeres, 5th World Congress of Gynaecology and Obstetrics, Sydney, 1967, p 348, Butterworths, Australia; see ref 16 for claim to series.

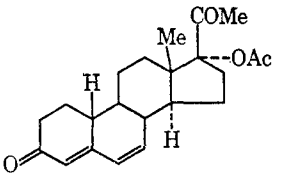
(87) L. Haberland, *Muenchen Med. Wochenschr.*, **68**, 1577 (1921).

(88) A. W. Makepeace, G. L. Weinstein, and M. H. Friedman, *Amer. J. Physiol.*, **119**, 512 (1937).

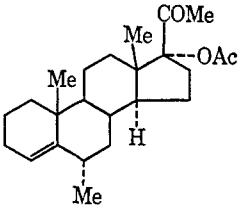
(89) R. Kurzrok, *J. Contraception*, **2**, 27 (1937).

(90) Quoted in editorial, *Hum. Fert.*, **10**, 80 (1945).

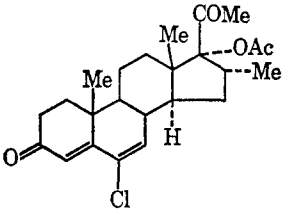
(91) J. Rock, C. R. Garcia, and G. Pincus, *Recent Progr. Horm. Res.*, **13**, 323 (1957).



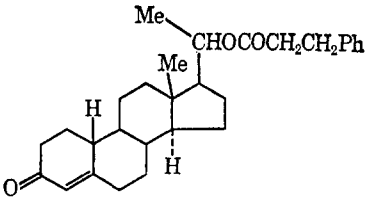
116
Ciba 31,458 Ba



117
Anagestone acetate



118
Clomegestone acetate



119
Xinogestone

orally active 19-norprogestagens, the group[92] turned its attention to norethynodrel (**22**), norethindrone (**19**), and 17α-ethyl-19-nortestosterone (**120**). By a fortuitous circumstance, early samples of two of these progestagens (**22** and **19**) were contaminated by estrogen[93] carried over from the Birch reduction of **1** (R = Me) employed for their preparation. Their study revealed[94] the superiority of the estrogen-containing preparations over the nonestrogenic progestagen (**120**) in controlling BTB. This observation provided the vital clue to the role of estrogen in cycle control and led to the development of presently available estrogen–progestagen combination products. Almost simultaneously, the sequential method predicted by Albright was developed[95] independently by groups led by Greenblatt and by Goldzieher. In this regimen, ovulation is inhibited by estrogen alone. Progestagen is added toward the end of each cycle of treatment, however, in order to enforce cycle control.

Estrogens alone are used to some extent as a postcoital pill[96] but are not satisfactory owing to troublesome side effects.

More recently, attention has been directed to the use of progestagens alone as contraceptive agents.[97] By suitably adjusting the dose and administering the product daily, these "minipills" have proved effective antifertility agents, with irregular bleeding as their main disadvantage.

Presently used contraceptive progestagens are conveniently classified as follows:

Progestagens without estrogenic and androgenic effects potent antiandrogens
Chlormadinone acetate
Megestrol acetate
Dimethisterone

Progestagens without estrogenic, androgenic, and antiandrogenic effects
Algestone acetophenide

Progestagens with slight androgenicity
Medroxyprogesterone acetate

Progestagens with some androgenicity
Norethindrone
Norethisterone acetate
Lynestrenol
Norgestrel
Quingestanol acetate

Progestagens with some estrogenic and slight androgenic properties
Ethynodiol diacetate

Estrogens with some progestational but no androgenic activity
Norethynodrel

By careful attention to the psychosomatic type of the patient, the physician can often select the product best suited to the woman. Regrettably, dosage based upon patient weight is still a dream of the future.

Acknowledgments. The impetus for this review was provided by the move from London, U. K., to Cincinnati, U. S. A. Fortuitously this coincided with completion of work on the older methods of fertility control reviewed above, thereby opening the way to the development of new concepts in response to the challenge of the new and vigorous environment. In closing this chapter, the reviewer is deeply conscious of the debt he owes to the close and loyal colleagues he had in the U. K. He is particularly indebted to Dr. Frank Hartley, C.B.E., who was Director of Research of "The British Drug Houses Ltd." up to 1962, and to Dr. Alan David, who so ably and enthusiastically provided at first the biological and latterly the clinical support for the reviewer's former group. *Consummatum est!*

(92) J. Rock, G. Pincus, and C. R. Garcia, *Science*, **124**, 891 (1956).
(93) See data provided by V. Drill, F. Saunders, and R. A. Edgren, and quoted by G. Pincus in *Recent Progr. Horm. Res.*, **13**, 343 (1956).
(94) G. Pincus, J. Rock, and C. R. Garcia, *Ann. N. Y. Acad. Sci.*, **71**, 677 (1958).
(95) See the review by V. Petrow, *Essays Biochem.*, **2**, 117 (1956), for a historical survey of this complex development.
(96) *Cf.* IPPF Medical Bulletin, 3 (3), Aug 1969, p 6.
(97) See the review by V. Petrow, *Chem. Brit.*, **6**, 167 (1970).